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INTELLECTUAL PROPERTY LAW
(PATENT, BIOTECHNOLOGY, COMPUTER, TRADEMARK & TRADE SECRET LAW)

October 12, 1999

FACSIMILE COVER SHEET

PLEASE DELIVER TO: Examiner Andrew Wang

COMPANY: U.S. PTO/ ART UNIT 1635

FACSIMILE NUMBER: (703) 308-4242

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FROM: Benjamin A. Adler

MESSAGE: Please deliver the attached to Examiner Wang. Attached is a Response after Final Office Action Under 37 CFR 1.116 for *Inhibition of Cationic Amino Acid Transporter and Uses Thereof*, Serial No: 09/238, 972 (MacLeod, C.L., D5232CIP).

cc: BAA.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#8 S.J. 10/12/99 (NB)

APPLICANT: MacLeod, C.L.	§	**ART UNIT: 1635**
FILED: January 27, 1999	§	**EXAMINER: A. Wang**
SERIAL NO.: 09/238,972	§	
FOR: Inhibition of Cationic Amino Acid Transporter and Uses Thereof	§	**DOCKET: D5232CIP3**

The Assistant Commissioner of Patents and Trademarks
BOX AF
Washington, DC 20231

Certificate of Facsimile Transmission

I certify that this response was transmitted via Facsimile to Examiner Andrew Wang at the Patent Office on the date indicated below.

Oct 12, 1999
Date

Benjamin Aaron Adler, Ph.D., J.D.

Please fax to Andy 10/18/99

RESPONSE UNDER 37 CFR 1.116

Dear Sir:

Responsive to the Final Office Action mailed August 13, 1999, please enter the following amendments and remarks. Reconsideration of the claims as amended is respectfully requested.

REMARKS

The 35 USC §102 Rejection

Claims 3, 16, and 17 remain rejected under 35 USC §102(b) as being anticipated by U.S. Patent No. **5,312,733** (**MacLeod**). This rejection is respectfully traversed.

The current application is a continuation in part of U.S. Patent Application Ser. No. 08/187,634, now **U.S. Patent 5,866,123** which is a continuation in part of U.S. Patent Application Ser No. 07/686,322, now **U.S. Patent 5,312,733** which is a continuation in part of U.S. Patent Application Ser No. 07/509,684, now abandoned. Thus, the instant application is a continuation in part U.S. Patent **5,312,733**. The Examiner, however, refuses to extend priority regarding antisense oligonucleotides to 07/686,322, now **U.S. Patent 5,312,733** because U.S. Patent Application Ser No. 07/686,322 describes the possibility of directing antisense oligonucleotides against the sequences of the instant invention while the intervening U.S. Patent Application Ser. No. 08/187,634 does not. The Examiner also argues that 08/187,634, fails to incorporate the contents of 08/686,322 by reference "thereby preventing priority status to the filing date of application 08/686,322." The Applicant respectfully disagrees.

First of all, the Applicant disputes that U.S. Patent Application Ser. No. 08/187,634, now **U.S. Patent 5,866,123**, fails to incorporate the contents of U.S. Patent Application Ser. No. 08/686,322 by reference. The rules for referencing prior applications [37 CFR 178 (2)] state:

> Any nonprovisional application claiming the benefit of one or more prior filed copending applications... must contain... in the first sentence of the specification following the title a reference to each such prior application, identifying it by application number... and indicating the relationship of the applications.

This requirement has been fulfilled by the first paragraph of U.S. Patent Application Ser. No. 08/187,634 under the heading "Cross Reference to Related Applications" which states:

> This application is a continuation-in-part of U.S. patent application Ser. No. 07/686,322, filed April 21, 1991, now U.S. Patent **5,312,733**, which is a continuation in part of U.S. patent application Ser No. 07/509,684, filed April 13, 1990, now abandoned

This reference has been placed in the first line of the specification of 08/187,634, now **U.S. Patent 5,866,123**, and thus satisfies this requirement. Based on this reference, the Applicant asserts that 08/187,634, now **U.S. Patent 5,866,123**, does indeed satisfactorily incorporate the contents of 08/686,322 by reference. Similarly, in the instant application applications, the requirement is satisfied on page 1, lines 11-16:

> This application is a continuation-in-part of U.S. Patent Application No. 08/187,634, filed January 26, 1994, which is a continuation-in-part of U.S. Patent Application No. 07/686,322, filed April 11, 1991, now U.S. Patent No. **5,312,733**, which is a continuation-in-part of U.S. Patent Application No. 07/509,684, filed April 13, 1990, now abandoned.

Therefore, the instant application also properly incorporates by reference the earlier applications. In addition, Section 201.11 of the Manual of Patent Examining Procedure states under "Copendency" that "the first application may contain more that the second application, or the second may contain more that the first, and in either case the second application is entitled to the benefit of the first as to the common subject matter. There is no requirement that an intervening application, or in other words "an application similarly entitled to the benefit of the filing date of first application," must contain all of the contents of the first applications in order that a later application be entitled to the benefit of those contents. Thus, a third application, entitled to the priority of the first application through a second application, can contain material provided in the first application, but not in the second, and still be entitled to the priority of the first application with regard to that material. If the Examiner intends to maintain the rejection of the priority of the instant invention based upon this premise, the Applicant respectfully requests that the Examiner cite the appropriate statutes or practice rules to this effect. Otherwise, the Applicant respectfully request that priority of the instant invention to U.S. Patent application 07/686,322, now U.S. Patent **5,312,733** and to U.S. Patent

Application Ser No. 07/509,684, now abandoned, be restored; and, accordingly, the Applicant requests that the rejection of claims 3, 16, and 17 as anticipated by U.S. Patent No. **5,312,733** under 35 USC §102(b) be withdrawn.

The 35 USC §112 Rejections

Claims 3 and 16 have been rejected under 35 USC §112, first paragraph, as "containing subject matter which was not described in the specification in such a way as convey to one skilled in the art that the inventor . . . had possession of the claimed invention." This rejection is respectfully traversed.

The first contention of the Examiner is that the specification does not enable the formation of other inhibitory antisense oligonucleotides. The Applicant respectfully disagrees. It is relatively easy for those skilled in the art to design antisense sequences that effectively inhibit the expression of a gene. While the current application does not list the entire open reading frame of *CAT2*, the current application is a continuation-in-part of application 08/187,634, now **U.S. Patent 5,866,123** which does list the entire sequence of the *CAT2* open reading frame. This sequence is also

given in **MacLeod** et al. Mol. Cell. Biol., 10:3663-3674 (1990) and is also available from GenBank as accession no. M32485.

From the CAT2 open reading frame sequence provided in the references listed above, it would be easy for one skilled in the art to design additional oligonucleotides which would inhibit CAT2 expression. While not every oligonucleotide derived from a DNA sequence will function as desired, numerous predictive computer programs are available to determine which oligonucleotides which will preferentially associate with the desired target sequences rather than themselves or exogenous sequences. The most effective regions to target in a gene (eg. the 5' end of the open reading frame) are well known to those skilled in the art. While the new oligonucleotides would need to be screened for effectiveness in inhibiting CAT2 expression, this would not constitute undue experimentation. The issue of what constitutes "undue" experimentation has been extensively discussed (see, e.g., *In re Wands*, 858 F.2d at 737; *In re Forman*, 230 USPQ at 547). In *In re Wands*, the court writes: "Enablement is not precluded by the necessity for some experimentation such as routine screening." (*Id.* at 736-737). With a small amount of screening, one skilled in the art could easily design other effective antisense oligonucleotides.

Since it is relatively easy for those skilled in the art to design antisense oligonucleotides to inhibit the expression of a given gene, it is less the design of the oligonucleotide and more the effect of the resulting inhibition of the *CAT2* gene that is important in the instant invention. The Applicant has clearly shown that overexpression of *CAT2* in Xenopus oocytes could be normalized with the antisense oligonucleotide. The Examiner argues that the specification does not provide any guidance regarding administration of "any type antisense oligo targeted to *CAT2* that would result in an ameliorative effect of any particular pathological state . . . [or] pathological condition by inhibiting CAT2." However, the result described in the specification show that the antisense oligonucleotide is capable of alleviating overexpression of *CAT2 in vitro*.

CAT2 regulates intracellular arginine accumulation. As nitric oxide is the sole precursor for nitric oxide synthesis, limitation of arginine transport will also result in an inhibition of nitric oxide production. Numerous diseases are know to have elevated nitric oxide levels as described on pages 4-8 of the specification. For example, nitric oxide is elevated in breast cancer and the degree of elevation correlates with the grade of the tumor (Page 4, lines 5-8). Therefore, it is highly likely that the instant invention would be

efficacious in the treatment of breast cancer. The Applicant respectfully requests that the rejection of claims 3 and 16 under 35 USC §112 be withdrawn.

Claims 1-9 and 16 remain rejected under 35 USC §112, first paragraph because the specification is "only enabling for claims limited to an antisense oligo consisting of SEQ ID No: 2 and a method of inhibiting CAT2 expression using said antisense oligonucleotide." The Examiner also continues to argue that no specific guidance is provided for application of the instant invention to any particular disease condition. This rejection is respectfully traversed.

The issue of whether one skilled in the art could easily design additional inhibitory antisense oligonucleotides has been discussed in depth above. The Applicant again asserts that it would be relatively easy for those skilled in the art to design additional antisense oligonucleotides from the sequence of the *CAT2* cDNA as given in **U.S. Patent 5,866,123; MacLeod** *et al.* Mol. Cell. Biol., 10:3663-3674 (1990); and, GenBank accession no. M32485. The Applicant respectfully reminds the Examiner that numerous predictive computer programs are available to help eliminate inherently troublesome oligonucleotides. The Examiner disputes that the 55% success rate of **Hoke** et al., is significant to the instant

invention. The mechanisms by which different genes are transcribed and translated are essentially identical. Thus, it would be logical that the mechanisms of inhibiting these processes from gene to gene would also be identical. If the Examiner disputes that this is the case, then it can also be argued that the difficulties identified in **Hoke** *et al.*, **Gerwitz** *et al.* (Proc. Natl. Acad. Sci. U.S.A., 93:31613163, 1996) and **Branch** (TIBS, 23:45-50, 1998) may not be applicable to the instant invention as well.

Nevertheless, the Applicant respectfully reasserts that the 55% success rate of **Hoke** et al., does suggest a similar rate of success for the instant invention as well. At such a rate of success, the necessary screening of the oligonucleotides for effectiveness would not constitute undue experimentation. With a small amount of screening, one skilled in the art could easily design other effective antisense oligonucleotides.

The Applicant has clearly shown that overexpression of *CAT2* in Xenopus oocytes could be normalized with an antisense oligonucleotide. This shows that a least part of the gene is physically available for antisense inhibition. As such the examiner, has not provided any compelling reason why it should be any more difficult to design additional antisense oligonucleotides for *CAT2* than it was

for **Hoke** *et al.* to design them for *ELAM-1* RNA. While some transcripts may be folded such that it is impossible an antisense molecule to access the transcript, the success of the one oligonucleotide attempted in the instant invention show that this is not the case for *CAT2*. The examiner has no proof that the design of additional antisense oligonucleotides for CAT2 would be difficult but is instead automatically assuming a worst case scenario when in fact the statistical chance that the applicant picked the one and only usable antisense oligonucleotide is astronomical.

The Examiner also continues to argue that the specification does not provide any guidance regarding administration of "any type antisense oligo targeted to CAT2 that would result in an ameliorative effect of any particular pathological state . . . [or] pathological condition by inhibiting CAT2." The Examiner previously argued (Office Action of April 13, 1999) that the clinical application of antisense is questioned since there are several obstacles that must be overcome such as degradation, molecular size and charge, bioavailability, and toxicity. As delivery methods improve, so will the efficiency of antisense therapy. The present invention neither makes any claims to any of these features nor does it claim to solve all problems with antisense technology--only that antisense

inhibition of CAT2 can restore arginine transport to normal levels and thus affect nitric oxide production.

Even though no specific instance of *in vivo* ameliorative effects are given in the specification, it cannot be disputed that the instant invention is useful in downregulating arginine transport and thus nitric oxide production. Since nitric oxide is such an important regulatory molecule, there can be no doubt that the instant application will have ameliorative effects *in vivo*. The applicant is not claiming to be able to cure the disease states listed in claims 6-9, only that the instant invention is likely to have some utility in treating the effects of these conditions since nitric oxide is known to play a role in the pathological mechanisms involved in these diseases.

In light of the extensive arguments discussed above, the applicant maintains that the invention is in fact enabled As such, the Applicant respectfully requests that the 35 USC §112 rejection of claims 1-9 and 16 be withdrawn.

This is intended to be a complete response to the Final Office Action mailed August 13, 1999. If any issues remain

outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: Oct 12, 1999

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